Epidemiology, Costs, Consequences, and Pathophysiology of Type 2 Diabetes: An American Epidemic

Lawrence Blonde, MD

Director, Diabetes Clinical Research Unit,
Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, LA

The prevalence of diabetes in the United States increased by 33% from 4.9% in 1990 to 6.5% in 1998. Presently almost 16 million Americans have diabetes mellitus, and the prevalence of diabetes is doubling every 10-15 years. More than 90% of diabetic patients have type 2 diabetes; about one third of patients with type 2 diabetes are not yet diagnosed. Diabetes is the number one cause of adult blindness, end-stage renal disease, and nontraumatic amputations in the US and is associated with a marked increase in atherosclerotic disease.

Diabetes is one of the most costly of medical conditions. In the US, 1 in every 7 health care dollars and 25% of the Medicare budget is spent on patients with diabetes. In 1997, total direct and indirect costs attributed to diabetes in the US were estimated at $98 billion. Substantial data suggest that glycemic control reduces morbidity and mortality as well as health care costs and improves quality of life and productivity.

Relatively new diagnostic criteria for diabetes lower the threshold for diagnosis from 140 to 126 mg/dL. The pathophysiology of type 2 diabetes must be considered in the formulation of treatment strategies. The majority of patients with type 2 diabetes have both insulin resistance and an insulin secretory deficit. While medical nutrition therapy and carefully prescribed exercise remain the cornerstones of treatment, most patients will require pharmacologic agents to achieve treatment goals. In fact, studies indicate that most patients will require combinations of antidiabetic agents with complementary mechanisms of action. Fortunately, many new antidiabetic agents available during the past several years provide more options for patients with type 2 diabetes.

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Diabetes mellitus is the name given to a group of metabolic disorders that are characterized by hyperglycemia and at least a relative deficiency of insulin. An international Expert Committee was established in May 1995 under the sponsorship of the American Diabetes Association (ADA) to review the classification and diagnostic criteria for diabetes mellitus. They scrutinized scientific data and ultimately proposed that both the classification and diagnostic criteria for diabetes mellitus be revised (1).

The new classification proposed by the Expert Committee is etiology based, unlike the World Health Organization (WHO) classification, which is both treatment and etiology based (2). The terms insulin-dependent diabetes mellitus and noninsulin dependent-diabetes mellitus have been replaced by the terms type 1 diabetes and type 2 diabetes. The committee chose to use Arabic rather than Roman numerals to differentiate the two since the latter can be misleading; for example, II may be mistaken for 11. The committee eliminated the term malnutrition-based diabetes mellitus, since the evidence supporting protein deficiency as a cause for diabetes was not convincing.

This article focuses primarily on the incidence and prevalence of type 2 diabetes, the most common form of diabetes mellitus. In addition, it will briefly present evidence for the benefit, effectiveness, and cost effectiveness of treatment of people with type 2 diabetes.

Prevalence of Diabetes Mellitus

The Centers for Disease Control (CDC) recently reported the results of the Behavioral Risk Factor Surveillance System survey which revealed that the prevalence of diabetes in the US had increased by 33% from 4.9% in 1990 to 6.5% in 1998; the increase in prevalence was highly correlated with the prevalence of obesity ($r=0.64$, $P<0.001$) (3). In addition to the known increase in the prevalence of type 2 diabetes in the elderly, type 2 diabetes is increasing in children and adolescents in areas with high proportions of at-risk ethnic groups. In 1992, type 2 diabetes accounted for 2%-4% of all childhood diabetes; by 1994, this number had increased to 16%. The increased incidence of type 2 diabetes in children may be due in part to increased obesity and decreased physical activity (4).

Presently almost 16 million Americans suffer from diabetes mellitus, and the prevalence of diabetes is doubling every 10-15 years (5). More than 90% of diabetic patients have type 2 diabetes, and about one third of patients with type 2 diabetes are not yet diagnosed.

Microvascular and Macrovascular Complications of Diabetes

Diabetes and its complications present a tremendous burden to the health care system. Diabetes is the number one cause of adult blindness (6), end-stage renal disease (7), and nontraumatic amputations in the United States (8). Moreover, diabetes is associated with a marked increase in the occurrence of atherosclerotic disease. Haffner and colleagues assessed the 7-year incidence of myocardial infarction (MI) among over 2400 subjects in a Finnish population-based study (8). Their results suggest that diabetic patients without previous MI have as high a risk of future MI as nondiabetic patients with previous MI. Moreover, subjects with both diabetes and a past history of MI had a 45% incidence of subsequent MI during the 7-year period of the investigation. Diabetic individuals also have increased incidence and prevalence of cerebrovascular and peripheral vascular disease, and their outcomes from all of these atherosclerotic disorders are inferior to those of subjects without diabetes (9).

Diabetes' Contribution to Health Care Costs

Largely due to these chronic complications, diabetes is one of the most costly of medical conditions. In the US, one in every seven health care dollars and 25% of the Medicare budget are spent on patients with diabetes (6). The total direct and indirect costs attributed to diabetes in the US were estimated at $98 billion in 1997 (10). As glycemic control worsens, health care costs increase. One study demonstrated a marked increase in health care costs with each 1% increase in baseline HbA1c: patients with an HbA1c of 10% had a 36% increase in 3-year medical costs compared with patients with an HbA1c of 6% (11).

Benefits of Glycemic Control

Substantial data suggest that glycemic control reduces morbidity and mortality as well as health care costs. The United Kingdom Prospective Diabetes Study (UKPDS) involved almost 4000 subjects with newly diagnosed type 2 diabetes who were randomized to conventional treatment with diet or intensive treatment with pharmacologic agents including two sulfonylureas or insulin. The study demonstrated a 25% decrease in risk of microvascular disease and a 12% decrease in risk of any diabetes-related endpoint with intensive glycemic control compared with conventional glycemic control ($P=0.0099$ and 0.029, respectively) (12). An epidemiologic analysis of all patients in the UKPDS also demonstrated significant reductions in the risk of complications with a 1% decrease in HbA1c, including a 37% reduction in microvascular endpoints ($P<0.0001$), a 14% decrease in MI and all-cause mortality, a 21% decrement in diabetes-related death, and a 43% reduction in amputations or death from peripheral vascular disease ($P<0.0001$) (13).

The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study demonstrated that improved glycemic control was associated with reduced cumulative mortality among patients with diabetes after an acute MI (14). This trial randomized 620 patients who had had an acute MI in the previous 24 hours and had a blood glucose concentration >11 mmol/L. Patients were allocated to either insulin-glucose infusion for 24 hours followed by subcutaneous insulin four times daily for ≥ 3 months or conventional therapy. After 1-year follow-up, the mortality rate in the intervention group was significantly reduced as compared with the placebo group (18.6% vs. 26.1%, relative risk reduction 29%, $P=0.027$). Therefore, the evidence suggests that improved glycemic control will reduce cardiovascular disease as well as microvascular disease in patients with diabetes.

Cost Effectiveness of Glycemic Control

Recent studies also attest to the cost effectiveness of diabetes care. An observational study by Wagner and colleagues in the Group Health Cooperative documented decreased health care utilization and cost among more than 700 patients who had a reduction in HbA1c of 1% or more compared with similar subjects with unimproved HbA1c levels (15). The UKPDS investigators have published a cost effectiveness analysis of their landmark intervention trial (16). The treatment that achieved improved outcomes in that study increased trial treatment costs by £695 per patient but reduced the cost of complications by £957 compared with conventional management. If standard practice visit patterns were assumed, the cost savings of intensive management was £479 per patient.

Yet, the UKPDS likely underestimated the cost benefits of improved glycemic control because the study did not include any

potential difference between groups in productivity losses or costs directly incurred by patients or their families. The CDC notes that hundreds of millions restricted-activity and bed days are due to acute and chronic conditions among persons with diabetes each year in the US (17).

Moreover, a study by Testa and Simonson demonstrated that improved glycemic control is also associated with benefits in symptoms, quality of life, and productivity (18). The authors randomized nearly 600 patients with type 2 diabetes to either a placebo or treatment with the antidiabetic agent, glipizide GITS. As expected, treated patients demonstrated substantial improvement in their glycemic control while the placebo-treated subjects showed some worsening. In addition to the assessment of glycemic control, the subjects in the study underwent an evaluation of their quality of life (QOL), which measures how people function in their daily lives. Using a diabetes-specific QOL survey instrument that they developed and validated, the authors noted that QOL treatment differences for symptom distress (SD units; +0.59, P<.001), general perceived health (+0.36, P= .004), cognitive functioning (+0.34, P=.005), and the overall visual analog scale (VAS; +0.24, P=.04) were significantly more favorable for active therapy.

The study also assessed some important economic outcomes. Favorable health economic outcomes for glipizide GITS-treated subjects included higher retained employment, measured as the percent relative to baseline of the number of subjects who worked $\geq$ 1 day in the previous week (97% vs. 85%, P<.001), and greater group productive capacity, measured as the percent relative to baseline of the days worked by subjects in each group in the previous week (99% vs. 87%, P<.001). At the end of week 15, 4.8% of the glipizide GITS-treated patients reported missing a half day or more of work during the previous week compared with 10.5% of the placebo-treated subjects. Similarly, the percentage of patients staying in bed for a half day or more or cutting down on usual activities was less in the glipizide GITS group (5.5% vs. 8.4% and 7.6% vs. 11.6%, respectively). Using 1995 US Census Bureau estimates of production losses for employed and unemployed males, the authors calculated less absenteeism losses ($24 vs. $115 per worker per month, P<.001), fewer bed-days losses ($1539 vs. $1843 per 1000 person-days, P=.05), and fewer restricted-activity days losses ($2660 vs. $4275 per 1000 person-days, P=.01) for subjects treated with glipizide GITS.

Patients reporting one or more nonstudy ambulatory care visits decreased from 38.9% to 27.7% in the glipizide GITS group (P=.002). This resulted in an estimated savings of $11 per patient per month (the authors assumed an average cost of $66 for an ambulatory visit). There was no significant change in the placebo-treated subjects.

This study achieved these marked benefits in only 16 weeks and makes the point that improved health care can be associated with both enhanced worker productivity and decreased utilization of medical services. The authors have provided evidence that by improving the health of workers, appropriate medical care can make an immensely important contribution to the economy. This contribution should be more regularly measured and considered when making judgments about the costs and benefits of therapies. In fact, their study likely underestimates the impact of improved glycemic control since there was no measure of the relative productivity of workers in the two groups during their work activities. One might suspect that diabetic subjects with poor glycemic control would be less productive than those enjoying good blood glucose control.

Pathophysiology of Type 2 Diabetes

The basic metabolic defects present in type 2 diabetes should be considered and addressed when selecting therapy. The pathophysiology of diabetes usually begins many years prior to diagnosis. Most patients have an increase in insulin resistance due to a genetic predisposition or aging, excess weight or body fat, and sedentary activity. As long as pancreatic beta cells can release enough insulin, glucose levels remain normal. However, as the beta cell defect gets worse, glucose levels rise. This is usually first manifest by a rise only in postchallenge glucose and patients have impaired glucose tolerance. As the beta cells continue to fail, glucose levels rise to levels allowing a diagnosis of diabetes to be made. As the beta cells continue to fail, glucose levels rise further (19).

Weyer and colleagues demonstrated the relative contribution of insulin resistance and beta cell dysfunction to the development of type 2 diabetes mellitus in a study of Pima Indians (19). As individuals progressed from normal glucose tolerance to impaired glucose tolerance, there was a significant decrease in insulin secretion. A further decrease in insulin secretion was associated with the progression to diabetes. Initially, insulin secretion declined by 27% in the progressors during the transition from normal glucose tolerance to impaired glucose tolerance, which demonstrates that defects in insulin secretion occur at an early stage in the development of type 2 diabetes. During the transition from impaired glucose tolerance to diabetes, insulin secretion decreased by an additional 57% for a total reduction of 78% from baseline.

In nondiabetic individuals, there is a basal secretion of insulin, which suppresses glucose production between meals and overnight. Basal insulin secretion is at nearly constant levels and represents about 50% of daily needs. In contrast, mealtime or prandial insulin secretion limits hyperglycemia after meals (20). There is an immediate rise and sharp peak at 1 hour (21). The prandial insulin secretion accounts for about 10% to 20% of daily needs at each meal.

Intavenous glucose infusions produce a biphasic insulin response in nondiabetic individuals. One of the first defects in beta cell function in type 2 diabetes is a selective loss of early or so-called

first phase insulin secretion in response to glucose (22). The resultant increase in postprandial glucose usually precedes the development of fasting hyperglycemia.

Diagnosing Diabetes Mellitus

The ADA Expert Committee revised diagnostic criteria for diabetes mellitus (1). The Table shows the new criteria for diagnosis. To be diagnosed with diabetes, a patient must have at least one out of any three criteria on 2 separate days. The ADA recommends that consideration be given to screening all individuals 45 years of age and older for type 2 diabetes. The recommended screening procedure is a laboratory-measured fasting plasma glucose, which, in clinical settings, is preferred over the oral glucose tolerance test (OGTT) due to ease of administration, convenience, patient acceptability, and lower cost. If the value is normal, repeat testing should be accomplished at 3-year intervals.

Furthermore, the ADA advises that clinicians consider testing individuals at a younger age and more frequently if they are at high risk for the subsequent development of type 2 diabetes. High-risk individuals include those who are obese (>120% desirable body weight or a body mass index >27 kg/m^2); have a first-degree relative with diabetes; are members of a high-risk ethnic population (e.g., African-American, Hispanic, Native American); have delivered a baby weighing >9 lb or have been diagnosed with gestational diabetes mellitus; are hypertensive (>140/90 mm Hg); have an HDL-C level <35 mg/dL or a triglyceride level >250 mg/dL; or have had impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous testing.

The Expert Committee on Diabetes also recognized the need to define a group of subjects with borderline glucose levels on the fasting plasma glucose (FPG) test and the OGTT. Patients with a FPG of ≥ 110 mg/dL (6.1 mmol/L) but < 126 mg/dL (7.0 mmol/L) were designated as having IFG. Patients who during a glucose tolerance test have a 2-hour glucose (2-h PG) value of ≥ 140 mg/dL (7.8 mmol/L) but < 200 mg/dL (11.1 mmol/L) have IGT. Many patients with IGT will also have IFG and vice versa. However, many other patients will qualify for only one of these two categories. An intriguing recent study suggests that the two groups may have somewhat different risks, with the IGT subjects appearing to have a greater risk of subsequent cardiovascular disease (23).

Moreover, while the FPG is recommended for screening for diabetes mellitus, Hermann et al assessed the utility of FPG and 2-hour glucose values during a standard OGTT using the National Health and Nutrition Examination Survey (NHANES III) data set. Only 8% of subjects were diagnosed by the FPG alone, 37% were diagnosed by both the FPG and 2-hour glucose levels, and fully 55% of individuals were diagnosed only with post-challenge glucose elevations (24). Thus, reliance on FPG for the diagnosis of diabetes differentially misses substantial numbers of subjects with isolated post-challenge hyperglycemia who have rates of microvascular complications (particularly diabetic retinopathy) and mortality similar to those of other diabetic subjects. A significant percentage of IFG subjects actually have type 2 diabetes on OGTT, and it may be reasonable to consider performing an OGTT in subjects with FPG values in the IFG range.

Table. Criteria for the diagnosis of diabetes mellitus.
[Reprinted from Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-1197.]

1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes mellitus include polyuria, polydipsia, and unexplained weight loss.

or

2. FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8h.

or

3. 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

OGTT = oral glucose tolerance test
WHO = World Health Organization

Treating Patients with Type 2 Diabetes

The ADA identifies a HbA1c of < 7% as a goal for glycemic control (25). However, some authorities believe that the glycemic goal in patients with type 2 diabetes should be plasma glucose levels as close to normal as possible without causing significant side effects in order to decrease associated complications (26). The epidemiologic analysis of the UKPDS demonstrated a decreasing occurrence of both microvascular and macrovascular endpoints with decreasing HbA1c values right down to normal values of 5.5% (13). There was a virtually linear relationship between HbA1c endpoint with no apparent threshold. Therefore, one could argue that the glycemic goal for patients with diabetes should be plasma glucose levels as close to normal as possible without causing significant side effects.

The ADA does not recommend postprandial glucose goals. However, some studies show that postprandial glycemia can be a better predictor of HbA1c than fasting glucose values (27). Moreover, focusing therapy only on fasting glycemia, as was done in the UKPDS, may not result in optimal control of HbA1c (12).

Treatment algorithms for patients with type 2 diabetes mellitus begin with medical nutrition therapy and carefully prescribed exercise. While studies demonstrate the efficacy of diet (28) and carefully prescribed exercise (29), most patients will require pharmacologic therapy to achieve glycemic goals. Fortunately, many new antidiabetic agents have become available during the past several years, providing more options for patients with type 2 diabetes. Other articles in this issue of the Journal focus in more detail on therapeutic strategies.

Summary

Type 2 diabetes mellitus is a serious, costly, and common disorder with a prevalence increasing at epidemic proportions. Improved glycemic control is proven to decrease the incidence of micro- and macrovascular complications and is cost effective. Virtually all patients have both insulin resistance and an insulin secretory defect at the time of diagnosis. The glycemic goal in patients with type 2 diabetes should be plasma glucose levels as close to normal as possible without causing significant side effects in order to decrease associated complications.

Medical nutrition therapy and appropriately prescribed increased activity are cornerstones of therapy. Most patients will require pharmacologic therapy and many therapeutic options are now available. Monotherapy is not usually effective in the long term. Physicians should follow screening recommendations for type 2 diabetes and prescribe whatever therapy is necessary to achieve glycemic goals in order to prevent or diminish the complications, lost productivity, and disability associated with diabetes.

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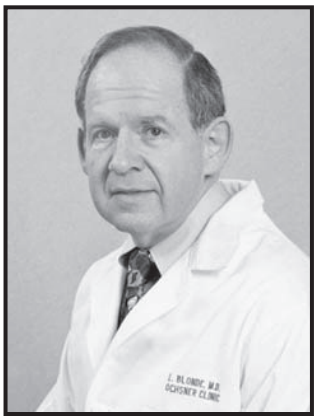

Dr. Blonde is on staff in Ochsner's Endocrinology Section.